REMARKS

Claims 1-56 were pending prior to this response, with claims 1-33 and 41-56 being withdrawn due to a restriction requirement. By the present communication, claim 57 has been added, claims 35-36 and 38-39 have been cancelled, and claims 34, 37, and 40 have been amended to define Applicants' invention with greater particularity. The claim amendments contained in this Supplemental Response replace the claim amendments contained in the Response mailed herein on February 3, 2004, which the Examiner indicates was non-responsive to the Office Action. The claim amendments add no new matter, being fully supported by the Specification and original claims. Accordingly, claims 1-34, 37, and 40-57 are currently pending.

The Objection to the Claims

The Examiner has objected to the claims as containing subject matter that is drawn to a non-elected invention, the elected claims 34-40 allegedly being drawn to "a method of identifying an agent that modulates the expression or activity of BACE1 by comparing the phenotype of a transgenic Aß1-42 organism contacted with the agent to that of a BACE-1 knockout organism. Applicants submit that the division of the claims was excessively confusing (claims 34-40 having been divided into no less than nine different groups) and resulted in inadvertent election of group XVIII (claims 34-40) rather than group XIV (claims 34 and 37-40). However, by amendment herein claims 35 and 36 have been cancelled and additional claim amendments have been introduced into claim 34 to recite that the phenotype of the BACE-1 knockout mouse is compared to the phenotype of a transgenic mouse that is transgenic in overexpression of Aβ1-42. Accordingly, Applicants respectfully that the claim amendments presented in this Supplemental Amendment limit the claims in accordance with the election of the group XIV subject matter as set forth in the restriction requirement. Therefore, Applicants respectfully request reconsideration and withdrawal of the objection to the claims in view of the restriction requirement.

The Objection to the Declaration

The Office Action indicates that the Declaration is objected to by the Examiner (page 1). However, no basis for the objection is stated, so Applicants are at a loss to know how to correct any defect in the Declaration that might be the basis for the objection. Clarification is respectfully requested.

The Rejection under 35 U.S.C. § 112, First Paragraph – Description

Applicants respectfully traverse rejection of claims 34-40 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 35-36 and 38-39 have been cancelled, rendering the rejection moot as to those claims. Therefore, Applicants will address the rejection as applied to claims 34, 37, 40 and 57.

Applicants disagree with the Examiner's assertion that the specification fails to contain sufficient description to provide those of skill in the art with the understanding that Applicant was in possession of the originally claimed invention because the specification describes only BACE1 knockout mice, and not other species of transgenic animals. In particular, Applicants disagree with the Examiner's assertion that the phenotype(s) of the claimed organisms cannot be predicted because the art of making knockout and transgenic organisms is highly unpredictable. Applicants respectfully submit that when function of a gene is disabled, production of the encoded protein ceases. Production of the encoded protein is a phenotype that can readily be measured by those of skill in the art, for instance, using an immunohistochemical approach.

However, to advance prosecution and reduce the issues, the pending claims have been amended to recite "a BACE1 knockout mouse" as the BACE1 knockout organism.
The Examiner acknowledges Applicants' description of a BACE1 knockout mouse is adequate to meet the description test of 35 U.S.C. § 112, first paragraph.

The Examiner further argues that the Specification fails to provide description of how to produce "a Aβ1-42 transgenic organism of any species" and that the transgenic organism of any species, including mouse, is unpredictable (Office Action, page 9).

However, Applicants submit that transgenic mice that express elevated levels of Aβ1-42 were known in the art as early as 1997 and are currently under development for commercial

distribution by The Jackson Laboratory, Bar Harbor, Maine (See attached printout from the Jackson Laboratory web site). Applicants' further submit that the making of transgenic mice was well developed at the filing of the present application and that those of skill in the art could readily produce such an organism, using the description describing the making of this particular transgenic mouse (i.e., Borchelt D. R., et al., *Neuron*. 1997 Oct; 19(4):939-45, abstract attached).

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection for alleged insufficient description of the subject matter of the claims under 35 U.S.C. § 112, first paragraph.

The Rejection under 35 U.S.C. § 112, First Paragraph – Enablement

Applicants respectfully traverse rejection of claims 34-40 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 35-36 and 38-39 have been cancelled, rendering the rejection moot as to those claims. Therefore, Applicants will address the rejection as applied to claims 34, 37, 40 and 57.

Applicants disagree with the Examiner's assertion that the specification fails to contain sufficient description to enable those of skill in the art to make a BACE1 knockout organism for any species other than mouse because ES cells are required to practice gene targeting by homologous recombination as disclosed in the subject application, but ES cells are not available for species other than mice. This ground of the rejection is supported by Leonard et. al., 1995; Campbell and Wilmut, Jan. 1997; and Mullins et al., 1996, none of which cites a reference published later than 1996. Applicants point out, however, that the priority date of the subject application is October 2000, and that ES cells of various species were known as of the priority date of the subject application (see, for example, U.S. Pat. No. 6,103,523, rabbit ES cells; U.S. Pat. No. 6,271,436, porcine ES cells (see, also, U.S. Pat. No. 6,194,635); U.S. Pat. No. 6,200,806, primate ES cells; and U.S. Pat. No. 6,107,543, bovine ES cells). Thus, it is submitted that the skilled artisan, viewing the subject application as of the time it was filed, would have known that ES cells of various species could be obtained and that homologous recombination could be used in such ES cells to generate various species of transgenic (e.g. knockout) non-

human animals. Accordingly, it is respectfully submitted that this ground of rejection should be removed.

However, to advance prosecution and reduce the issues, Applicants have amended the currently presented claims to limit the transgenic animals to a "BACE1-knockout mouse" and "a transgenic mouse that is transgenic for overexpression of Aβ1-42. The Examiner relies on M. Staufenbiel et al. as teaching that BACE1-knockout mice do not display the "phenotype" of cleaved Aβ peptides. However, the only result of the BACE1-knockout in the transgenic mouse as recited in the currently amended claims is a substantial decrease in expression or activity of BACE1 protein (See Specification, ¶ [0157]) in mouse brain (See Example 7). The results of Applicants tests indicate that in wild-type mouse BACE1 protein expression is particularly localized to the brain, particularly to pre-synaptic terminals (¶ [0188]); while BASE1 expression is substantially absent in the brain of a BASE1 knockout mouse. The Specification further identifies the absence of Aβ1-42, especially in the brain tissue, is a characteristic of a BASE1 knockout mouse. Thus, Applicants respectfully submit that a test agent that reduces the level of production of Aβ1-42, especially in the brain of *a transgenic mouse that is transgenic for overexpression of Aβ1-42* will be one that is a good candidate and merits further testing for utility in treatment of diseases associated with ß-amyloid production in humans, such as Alzheimer's disease.

In view of the claim amendments and the above remarks, Applicants respectfully submit that that subject matter of amended claims 34, 37, and 40 and new claim 57 is fully enabled under 35 U.S.C. § 112, first paragraph, and reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 34-40 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite due to use of the term "substantially equal" in claim 34. Applicants submit that the U.S. Court of Appeals for the Federal Circuit recently upheld use of "substantially" in claim language (Deering Precision Instruments L.L.C. v. Vector Distribution Systems Inc., CAFC, 10/17/03) (USPQ2d, Vol. 68, No. 7, 1716). In addition, there

is a long history of acceptance of the term "substantially" in claim language. Therefore, Applicants submit that, as used in claim 34, the term "substantially equal" meets the definiteness test under 35 U.S.C. § 112, second paragraph. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims for alleged indefiniteness as applied to present claims 34, 37, 40 and 57.

In summary, for the reasons set forth herein, Applicants maintain that claims 34, 37, 40 and 57 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

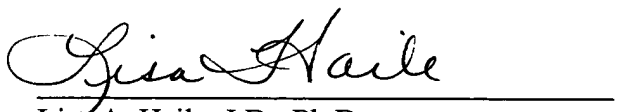
If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456.

Information Disclosure Statement Mailed April 9, 2003

Applicants bring to the Examiner's attention the Information Disclosure Statement (IDS) mailed April 9, 2003 and respectfully requests that the Examiner return an initialed copy of the Form PTO-1449 that was attached thereto, with the next Communication in this case.

Respectfully submitted,

Date: May 17, 2004



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San Diego, California 92121-2133
USPTO CUSTOMER NO. 28213

Attachments: Printout from the Jackson Laboratory web site (4 pgs.)
Abstract of Borchelt D. R., et al., *Neuron*. 1997 Oct; 19(4):939-45 (1 pg.)

JAX® Mice Data Sheet

Go to JAX® Mice Query Form

Strain Name: B6C3-Tg(APP695)3Dbo Tg(PSEN1)5Dbo/J
Stock Number: 003378

Price and Supply Information
General Terms and Conditions of Sale

Former Name B6C3-Tg(APP695)3Dbo Tg(PSEN1)5Dbo (Changed: 03-dec-2003)

Symbol(s) ***APP695***; ***PSEN1***;

Product Information
Strain Details

Type	JAX® GEMM® Strain - Transgene; Additional information on JAX® GEMM® Strains.
TJL Mating System	Other - see Colony Maintenance comment
Promoter	*Prnp*, prion protein promoter, mouse
Investigator - Mutation Made By	Dr. David R. Borchelt, The Johns Hopkins Univ School of Med
Investigator - Donating	Dr. David R. Borchelt, The Johns Hopkins Univ School of Med
Backcross Generation	F1 (09-oct-2003)

Strain Description
These transgenic mice express human presenilin 1 (A246E variant) and a chimeric amyloid precursor protein (APP_{Swe}). The mouse prion protein promoter directs expression of both transgenes. Elevated levels of the AB1-42(43) peptide is detected in brain homogenates. By nine months of age, histological examination of brain tissue reveals numerous amyloid deposits resembling those observed in the brains of patients with Alzheimer's disease (AD). The number of amyloid deposits increases dramatically between the ages of 10 and 12 months. These mice provide a useful model for studying the underlying mechanism of amyloid deposition, a process implicated in AD.

Strain Development
Mouse pronuclei (B6C3H) were injected with an expression plasmid containing a mouse prion promoter and a cDNA encoding human presenilin 1 bearing the A246E substitution (line N-5). Another subset of mouse pronuclei (B6C3H) were injected with an expression plasmid containing a cDNA encoding a chimeric amyloid beta (A4)

precursor protein, also regulated by the mouse prion promoter (line C3-3). The chimeric APP molecule was created by replacing sequences encoding the Abeta domain of the murine sequence with the cognate sequences of the human gene (mutations K595N, M596L). The two transgenic lines were subsequently mated to generate the double transgenic.

Gene Details

Symbol *APP695*
Symbol Name amyloid beta (A4) precursor protein (chimeric)
Chromosome UN
Symbol Common Name(s) APP PDGFB; FAD; amyloid; chimeric mouse/human beta-amyloid precursor protein;

Symbol *PSEN1*
Symbol Name presenilin 1 (Human)
Chromosome 14
Symbol Common Name(s) AD3, presenilin 1 (Alzheimer disease 3); FAD; PS1; S182; chimeric mouse/human beta-amyloid precursor protein;
Symbol Description (Human) Genome Database entry

Control Information

Symbol	Control
	B6C3FeF1/J *a/a* 001022

Considerations for Choosing Controls
Control Pricing Information for JAX® GEMM® Strains

Genotyping Protocols

Tg(APP695)
Tg(PSEN1)

Related Strains

004462 B6C3-Tg(APPswe,PSEN1dE9)85Dbo/J
003375 C3B6-Tg(APP695)3Dbo/J

Research Applications

This mouse can be used to support research in many areas including:

APP695 related

Mouse/Human Gene Homologs

Alzheimer's

Neurobiology Research
Alzheimer's Disease
Neurodegeneration

References

Primary Reference

Borchelt DR, Ratovitski T, van Lare J, Lee MK, Gonzales V, Jenkins NA, Copeland NG, Price DL, Sisodia SS. 1997. Accelerated amyloid deposition in the brains of transgenic mice coexpressing mutant presenilin 1 and amyloid precursor proteins. Neuron 19 :939-45. [PubMed: 9354339]

Additional References

Price and Supply Information

This strain is currently Under Development for Distribution Colony.
To register your interest in this strain go to Strain Interest Form.

To View All Strains Under Development go to REGISTER INTEREST: New Strains Under Development.

Estimated Available for Sale Date: 21-jun-2004

Please note: *Estimated available for sale dates are provided to keep customers better informed on strains under development. Please note that our Colony Managers routinely monitor the target date and edit it based on breeding performance and other factors. The length of time it takes to make a new strain available for sale depends on genotype, age, number of animals sent by the Donating Investigator, breeding performance, additional strain development (backcrossing, making homozygous), and anticipated demand for the strain/interest registered.*

Supply Details

Standard Supply	Level 10: Under Development for Distribution Colony.
Supply Notes	The stock is included in the Induced Mutant Resource collection.
Licensing	See **General Terms and Conditions of Sale** below for Licensing and Use Restrictions.
Control Information	View Control Information in Strain Details. View Control Pricing Information for JAX® GEMM® Strains.

General Terms and Conditions of Sale

View JAX® Mice Conditions of Use.

Use restrictions apply, see Policy on Licensing and Use Restrictions.

The Jackson Laboratory's Genotype Promise

The Jackson Laboratory has rigorous genetic quality control and mutant gene genotyping programs to ensure the genetic background of JAX® Mice strains as well as the genotypes of strains with identified molecular mutations. JAX® Mice strains are only made available to researchers after meeting our standards. However, the phenotype of each strain may not be fully characterized and/or captured in the strain data sheets. **Therefore, we cannot guarantee a strain's phenotype will meet all expectations.** To ensure that JAX® Mice will meet the needs of individual research projects or when requesting a strain that is new to your research, we suggest ordering and performing tests on a small number of mice to determine suitability for your particular project.

Ordering and Purchasing Information

Purchasing Information
JAX® Mice Orders
Surgical Services

Contact Information

Orders & Technical Support
Tel: 800.422.MICE (6423) or 207.288.5845
Fax: 207.288.6150
Technical Support Express E-Mail Form

Go to JAX® Mice Query Form

1: Neuron. 1997 Oct;19(4):939-45. Related Articles, Links

Accelerated amyloid deposition in the brains of transgenic mice coexpressing mutant presenilin 1 and amyloid precursor proteins.

Borchelt DR, Ratovitski T, van Lare J, Lee MK, Gonzales V, Jenkins NA, Copeland NG, Price DL, Sisodia SS.

Department of Pathology, Johns Hopkins School of Medicine, Baltimore, Maryland 21205, USA.

Missense mutations in two related genes, termed presenilin 1 (PS1) and presenilin 2 (PS2), cause dementia in a subset of early-onset familial Alzheimer's disease (FAD) pedigrees. In a variety of experimental in vitro and in vivo settings, FAD-linked presenilin variants influence the processing of the amyloid precursor protein (APP), leading to elevated levels of the highly fibrillogenic Abeta1-42 peptides that are preferentially deposited in the brains of Alzheimer Disease (AD) patients. In this report, we demonstrate that transgenic animals that coexpress a FAD-linked human PS1 variant (A246E) and a chimeric mouse/human APP harboring mutations linked to Swedish FAD kindreds (APP swe) develop numerous amyloid deposits much earlier than age-matched mice expressing APP swe and wild-type Hu PS1 or APP swe alone. These results provide evidence for the view that one pathogenic mechanism by which FAD-linked mutant PS1 causes AD is to accelerate the rate of beta-amyloid deposition in brain.

PMID: 9354339 [PubMed - indexed for MEDLINE]